Forum on Informatics Solutions
December 3, 2004

From *terminology* integration to *information* integration

An example in the domain of genomics

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Outline

- Background
  - Terminology integration:
    The Unified Medical Language System
  - Information integration:
    Genomics as an example
- Applications
  - GenesTrace
  - BioMeKe

Terminology integration

The Unified Medical Language System

Motivation

- Started in 1986
- National Library of Medicine
- "Long-term R&D project"
- Complementary to IAIMS (Integrated Academic Information Management Systems)

«[…] the UMLS project is an effort to overcome two significant barriers to effective retrieval of machine-readable information.

- The first is the variety of ways the same concepts are expressed in different machine-readable sources and by different people.
- The second is the distribution of useful information among many disparate databases and systems.»

Source Vocabularies (2004AB)

- 134 source vocabularies
  - 126 contributing concept names
- 73 families of vocabularies
  - multiple translations (e.g., MeSH, ICPC, ICD-10)
  - variants (American-English equivalents, Australian extension/adaptation)
  - subsequent editions usually considered distinct families (ICD: 9-10; DSM: IIIR-IV)
- Broad coverage of biomedicine
- Common presentation

Biomedical terminologies

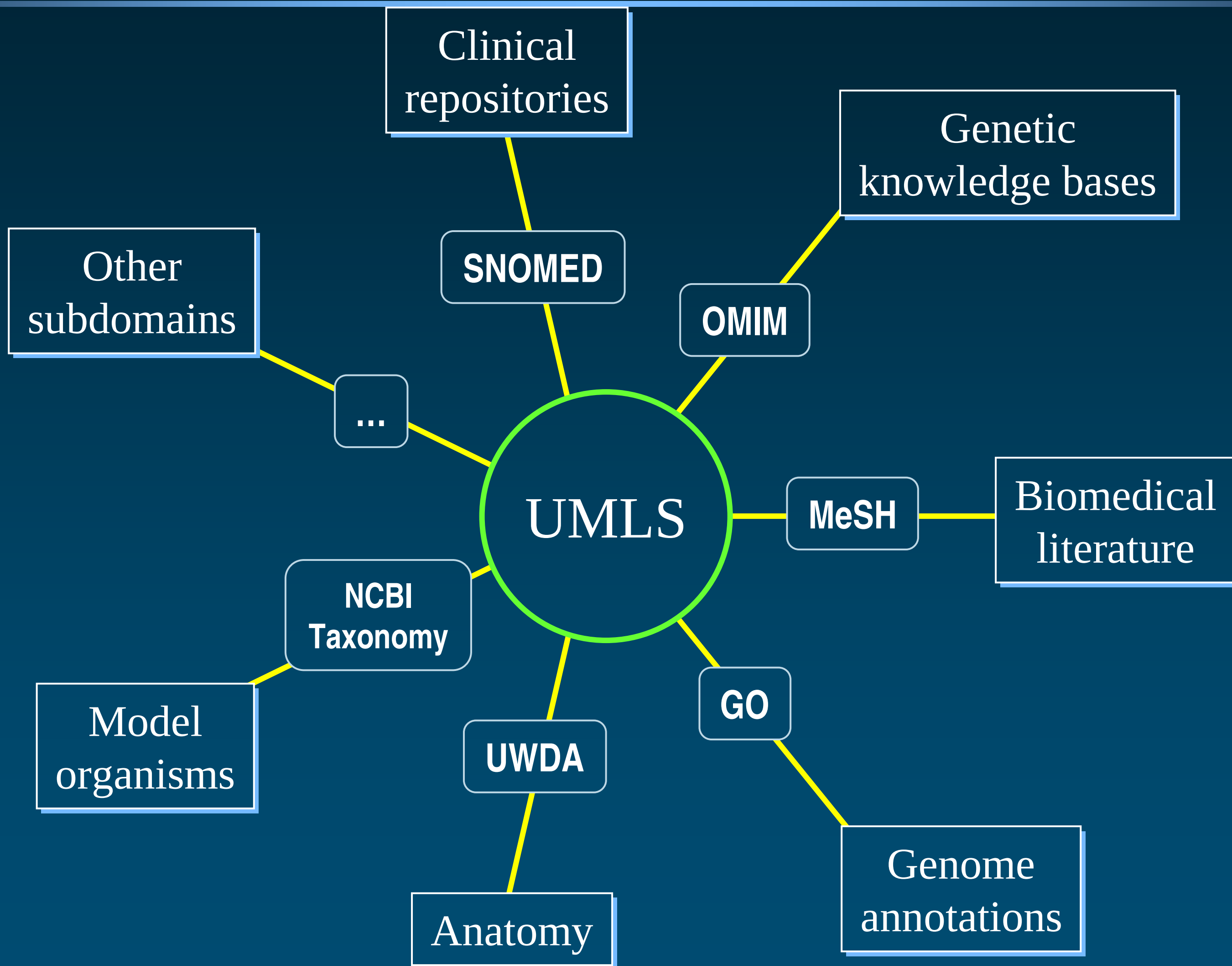
- General vocabularies
  - anatomy (UWDA, Neuronames)
  - drugs (RxNorm, First DataBank, Micromedex)
  - medical devices (UMD, SPN)
- Several perspectives
  - clinical terms (SNOMED CT)
  - information sciences (MeSH, CRISP)
  - administrative terminologies (ICD-9-CM, CPT-4)
  - data exchange terminologies (HL7, LOINC)

Biomedical terminologies (cont'd)

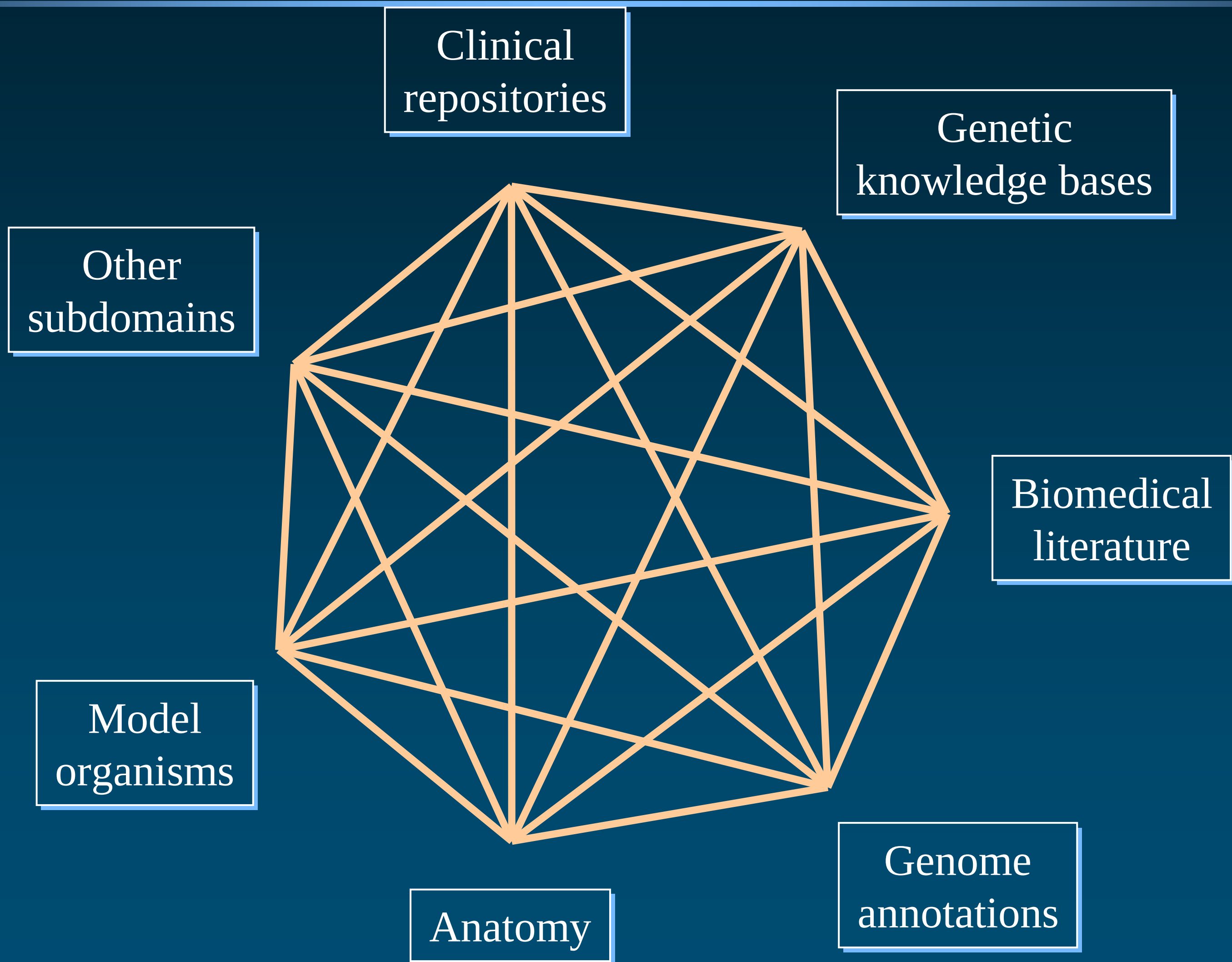
- Specialized vocabularies
  - nursing (NIC, NOC, NANDA, Omaha, PCDS)
  - dentistry (CDT)
  - psychiatry (DSM, APA)
  - adverse reactions (COSTART, WHO ART)
  - primary care (ICPC)
  - genomics (GO, OMIM, HUGO)
- Terminology of knowledge bases (AI/Rheum, DXplain, QMR)

The UMLS serves as a vehicle for the regulatory standards (HIPAA, CHI)

Integrating subdomains



Integrating subdomains



UMLS: 3 components

- Metathesaurus
  - Concepts
  - Inter-concept relationships
- Semantic Network
  - Semantic types
  - Semantic network relationships
- Lexical resources
  - SPECIALIST Lexicon
  - Lexical tools

Addison’s Disease: Concept

Disease or Syndrome

Addison’s Disease

ADRENAL INSUFFICIENCY (ADDISON'S DISEASE)
ADRENOCORTICAL INSUFFICIENCY, PRIMARY FAILURE
Addison melanoderma
Melasma addisonii
Primary adrenal deficiency
Asthenia pigmentosa
Bronzed disease
Insufficiency, adrenal primary
Primary adrenocortical insufficiency
Addison's, disease

MALADIE D'ADDISON - French
Addison-Krankheit - German
Morbo di Addison - Italian
DOENCA DE ADDISON - Portuguese
ADDISONOVA BOLEZN' - Russian
ENFERMEDAD DE ADDISON - Spanish

SNOMED
MeSH
AOD
Read Codes
…

C0001403

A disease characterized by hypotension, weight loss, anorexia, weakness, and sometimes a bronze-like melanotic hyperpigmentation of the skin. It is due to tuberculosis- or autoimmune-induced disease (hypofunction) of the adrenal glands that results in deficiency of aldosterone and cortisol. In the absence of replacement therapy, it is usually fatal.

Metathesaurus Concepts (2004AB)

- Concept (> 1M) CUI
  - Set of synonymous concept names
- Term (> 3.8 M) LUI
  - Set of normalized names
- String (> 4.3M) SUI
  - Distinct concept name
- Atom (> 5.1M) AUI
  - Concept name in a given source

A0000001 headache (source 1)
A0000002 headache (source 2)
S0000001

A0000003 Headache (source 1)
A0000004 Headache (source 2)
S0000002

L0000001

A0000005 Cephalgia (source 1)
S0000003

L0000002

C0000001

Cluster of synonymous terms

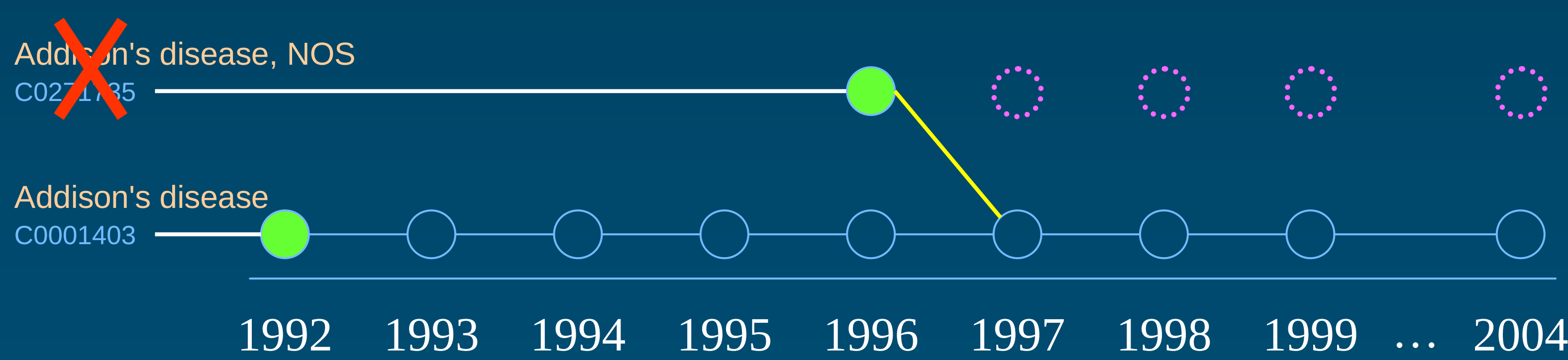
Concept
C0001621

Term L0001621	S0011232 *Adrenal Gland Diseases* S0011231 Adrenal Gland Disease S0000441 Disease of adrenal gland S0481705 Disease of adrenal gland, NOS S0220090 Disease, adrenal gland S0044801 Gland Disease, Adrenal	[…]
Term L0041793	S0860744 *Disorder of adrenal gland, unspecified* S0217833 Unspecified disorder of adrenal glands	
Term L0161347	S0225481 *ADRENAL DISORDER* S0627685 DISORDER ADRENAL (NOS)	[…]
Term L0181041	S0632950 *Disorder of adrenal gland* S0354509 Adrenal Gland Disorders	[…]
Term L0368399	S0586222 *Adrenal disease* S0466921 ADRENAL DISEASE, NOS	[…]
Term L1279026	S1520972 *Nebennierenkrankheiten*	GER
Term L0162317	S0226798 *SURRENALE, MALADIES*	FRE

[…]

Metathesaurus Evolution over time

- Concepts never die (in principle)
  - CUIs are permanent identifiers
- What happens when they do die (in reality)?
  - Concepts can merge or split
  - Resulting in new concepts and deletions



Metathesaurus Relationships

- Symbolic relations: ~9 M pairs of concepts
- Statistical relations : ~7 M pairs of concepts (co-occurring concepts)
- Mapping relations: 100,000 pairs of concepts

- Categorization: Relationships between concepts and semantic types from the Semantic Network

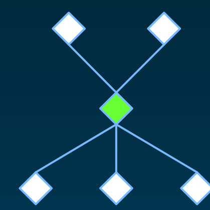
Symbolic relations

- Relation
  - Pair of “atom” identifiers
  - Type
  - Attribute (if any)
  - List of sources (for type and attribute)
- Semantics of the relationship:
  defined by its type [and attribute]

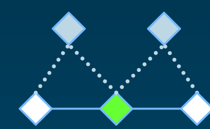
Source transparency: the information is recorded at the “atom” level

Symbolic relationships Type

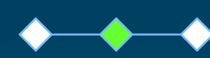
- Hierarchical
  - Parent / Child — **PAR/CHD**
  - Broader / Narrower than — **RB/RN**



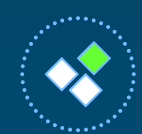
- Derived from hierarchies
  - Siblings (children of parents) — **SIB**



- Associative
  - Other — **RO**

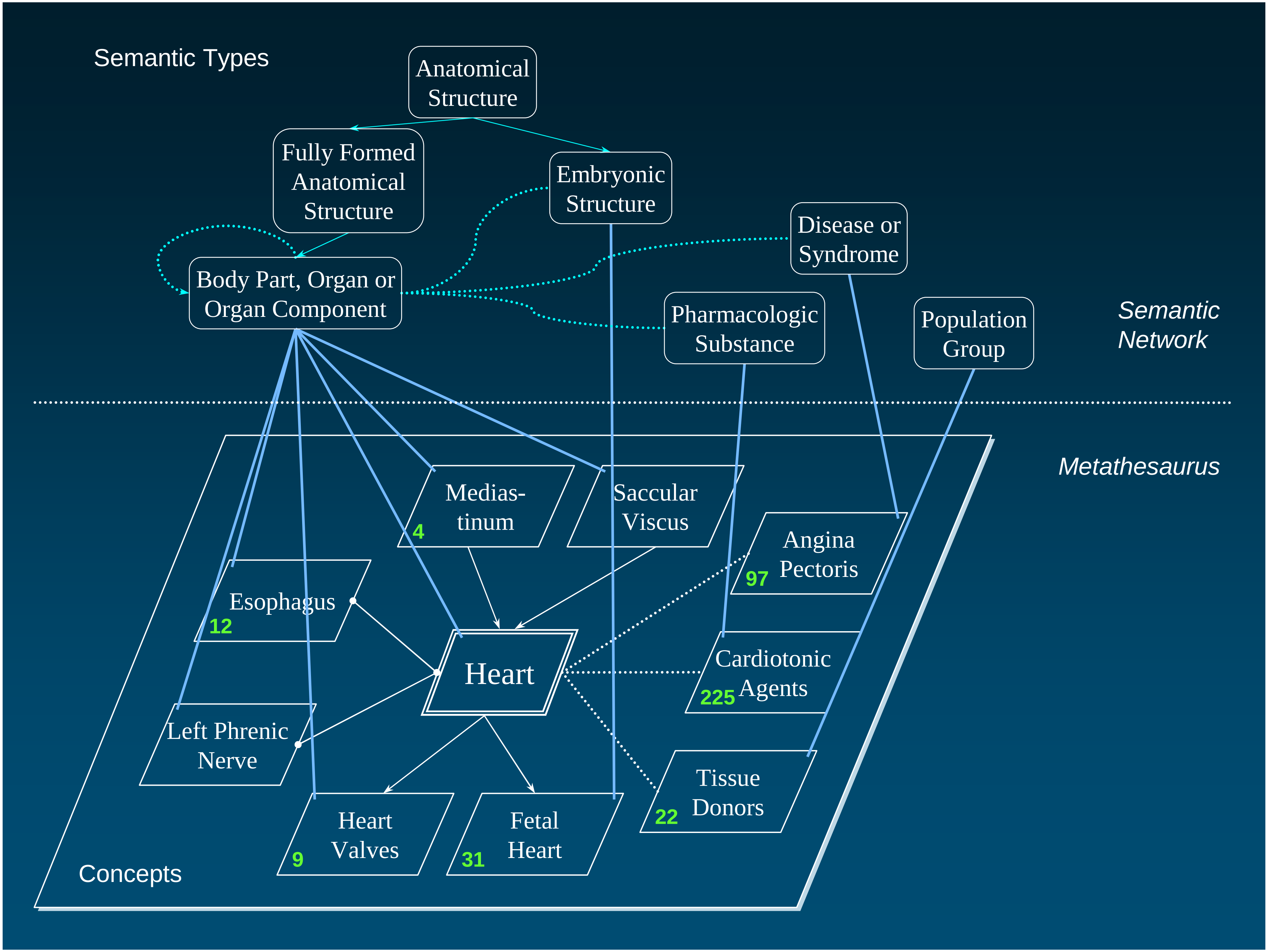


- Various flavors of near-synonymy
  - Similar — **RL**
  - Source asserted synonymy — **SY**
  - Possible synonymy — **RQ**



Symbolic relationships Attribute

- Hierarchical
  - isa (is-a-kind-of)
  - part-of
- Associative
  - location-of
  - caused-by
  - treats
  - …
- Cross-references (mapping)



Semantic Types
Anatomical Structure
Fully Formed Anatomical Structure
Embryonic Structure
Body Part, Organ or Organ Component
Disease or Syndrome
Pharmacologic Substance
Population Group
Semantic Network
Metathesaurus
Medias- tinum
4
Saccular Viscus
Angina Pectoris
97
Esophagus
12
Heart
Cardiotonic Agents
225
Left Phrenic Nerve
Tissue Donors
22
Heart Valves
9
Fetal Heart
31
Concepts

Lexical tools

- To manage lexical variation in biomedical terminologies
- Major tools
  - Normalization
  - Indexes
  - Lexical Variant Generation program (lvg)
- Based on the SPECIALIST Lexicon
- Used by noun phrase extractors, search engines

Normalization

	Hodgkin's diseases, NOS
Remove genitive	Hodgkin diseases, NOS
Remove stop words	Hodgkin diseases,
Lowercase	hodgkin diseases,
Strip punctuation	hodgkin diseases
Uninflect	hodgkin disease
Sort words	disease hodgkin

Normalization: Example

Hodgkin Disease
HODGKINS DISEASE
Hodgkin's Disease
Disease, Hodgkin's
Hodgkin's, disease
HODGKIN'S DISEASE
Hodgkin's disease
Hodgkins Disease
Hodgkin's disease NOS
Hodgkin's disease, NOS
Disease, Hodgkins
Diseases, Hodgkins
Hodgkins Diseases
Hodgkins disease
hodgkin's disease
Disease, Hodgkin

normalize → disease hodgkin

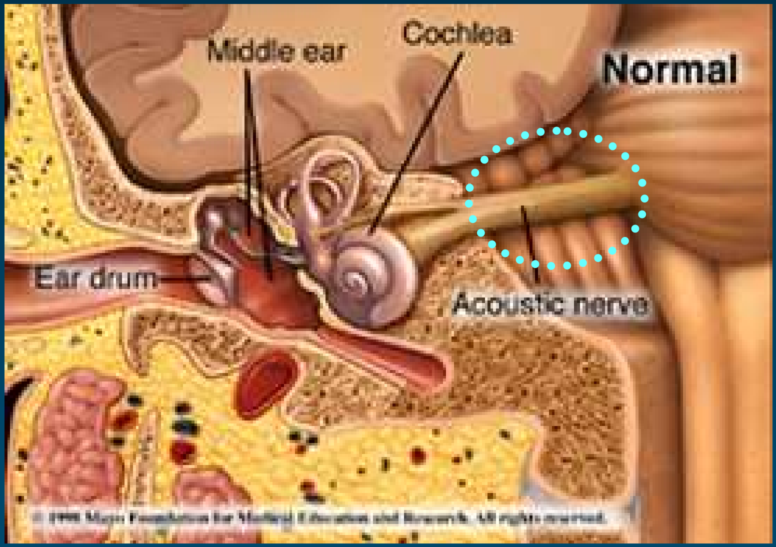
Information integration

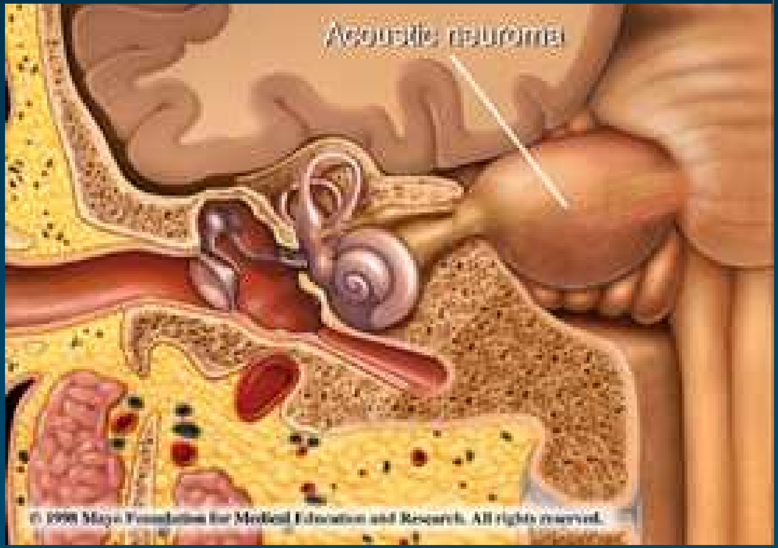
Genomics as an example

NF2 Gene, protein, and disease

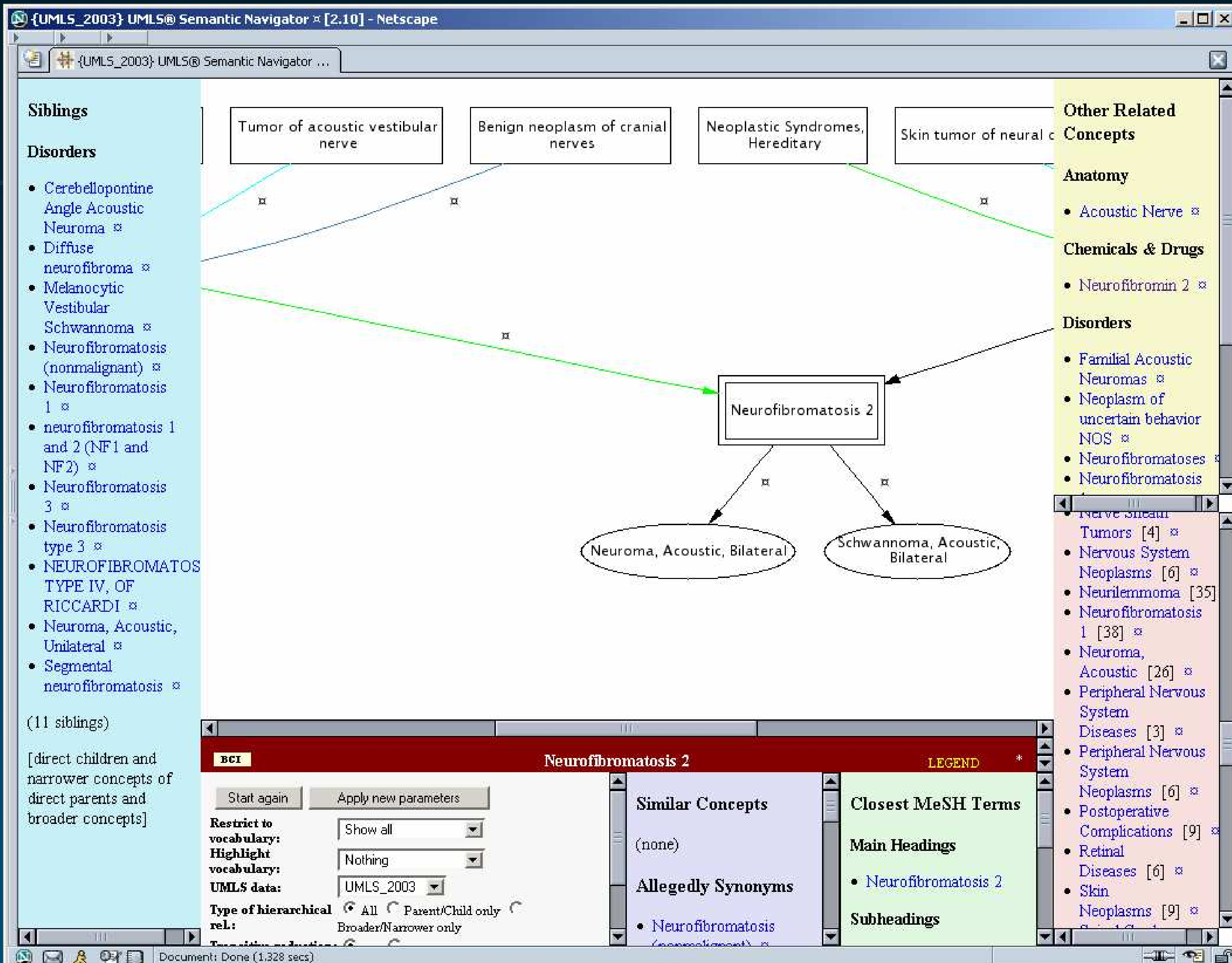
Neurofibromatosis 2 is an autosomal dominant disease characterized by tumors called schwannomas involving the acoustic nerve, as well as other features. The disorder is caused by mutations of the *NF2 gene* resulting in absence or inactivation of the protein product. The protein product of NF2 is commonly called *merlin* (but also neurofibromin 2 and schwannomin) and functions as a tumor suppressor.

Schwannoma (acoustic neuroma)

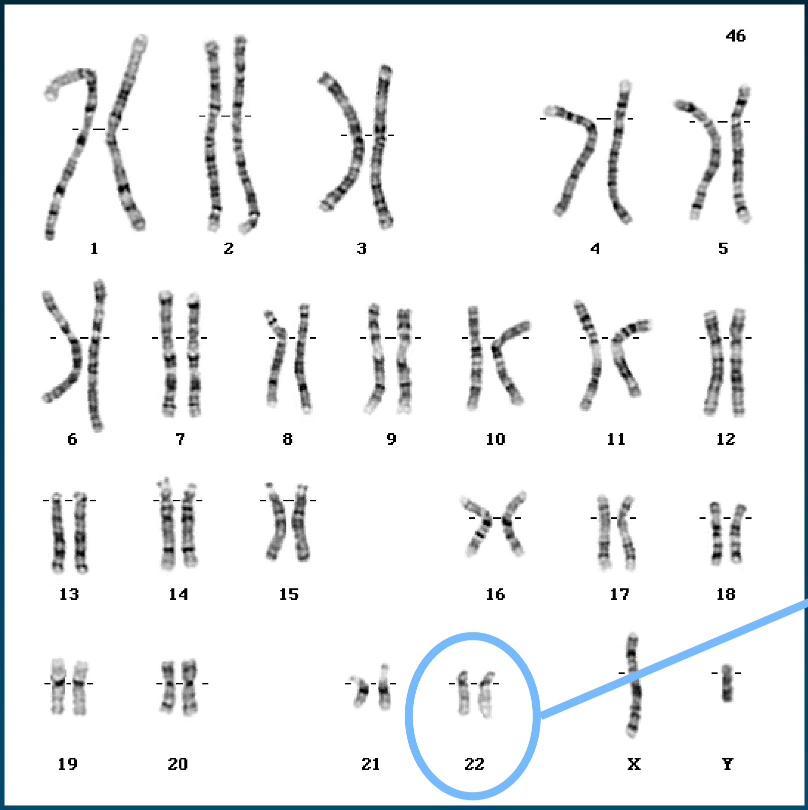




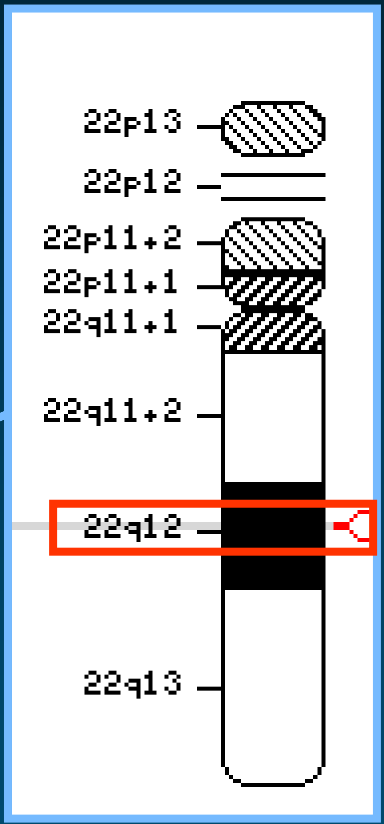
http://www.mayoclinic.com


{UMLS_2003} UMLS® Semantic Navigator ¤ [2.10] - Netscape
{UMLS_2003} UMLS® Semantic Navigator ...
Siblings
Disorders
Cerebellopontine Angle Acoustic Neuroma ¤
Diffuse neurofibroma ¤
Melanocytic Vestibular Schwannoma ¤
Neurofibromatosis (nonmalignant) ¤
Neurofibromatosis 1 ¤
neurofibromatosis 1 and 2 (NF1 and NF2) ¤
Neurofibromatosis 3 ¤
Neurofibromatosis type 3 ¤
NEUROFIBROMATOS TYPE IV, OF RICCARDI ¤
Neuroma, Acoustic, Unilateral ¤
Segmental neurofibromatosis ¤
(11 siblings)
[direct children and narrower concepts of direct parents and broader concepts]
Tumor of acoustic vestibular nerve
Benign neoplasm of cranial nerves
Neoplastic Syndromes, Hereditary
Skin tumor of neural c
Neurofibromatosis 2
Neuroma, Acoustic, Bilateral
Schwannoma, Acoustic, Bilateral
Other Related Concepts
Anatomy
Acoustic Nerve ¤
Chemicals & Drugs
Neurofibromin 2 ¤
Disorders
Familial Acoustic Neuromas ¤
Neoplasm of uncertain behavior NOS ¤
Neurofibromatoses
Neurofibromatosis
Tumors [4] ¤
Nervous System Neoplasms [6] ¤
Neurilemmoma [35]
Neurofibromatosis 1 [38] ¤
Neuroma, Acoustic [26] ¤
Peripheral Nervous System Diseases [3] ¤
Peripheral Nervous System Neoplasms [6] ¤
Postoperative Complications [9] ¤
Retinal Diseases [6] ¤
Skin Neoplasms [9] ¤
BCI
Neurofibromatosis 2
LEGEND
Start again
Apply new parameters
Restrict to vocabulary:
Show all
Highlight vocabulary:
Nothing
UMLS data:
UMLS_2003
Type of hierarchical rel.:
All
Parent/Child only
Broader/Narrower only
Similar Concepts
(none)
Allegedly Synonyms
Neurofibromatosis
Closest MeSH Terms
Main Headings
Neurofibromatosis 2
Subheadings
Document: Done (1.328 secs)

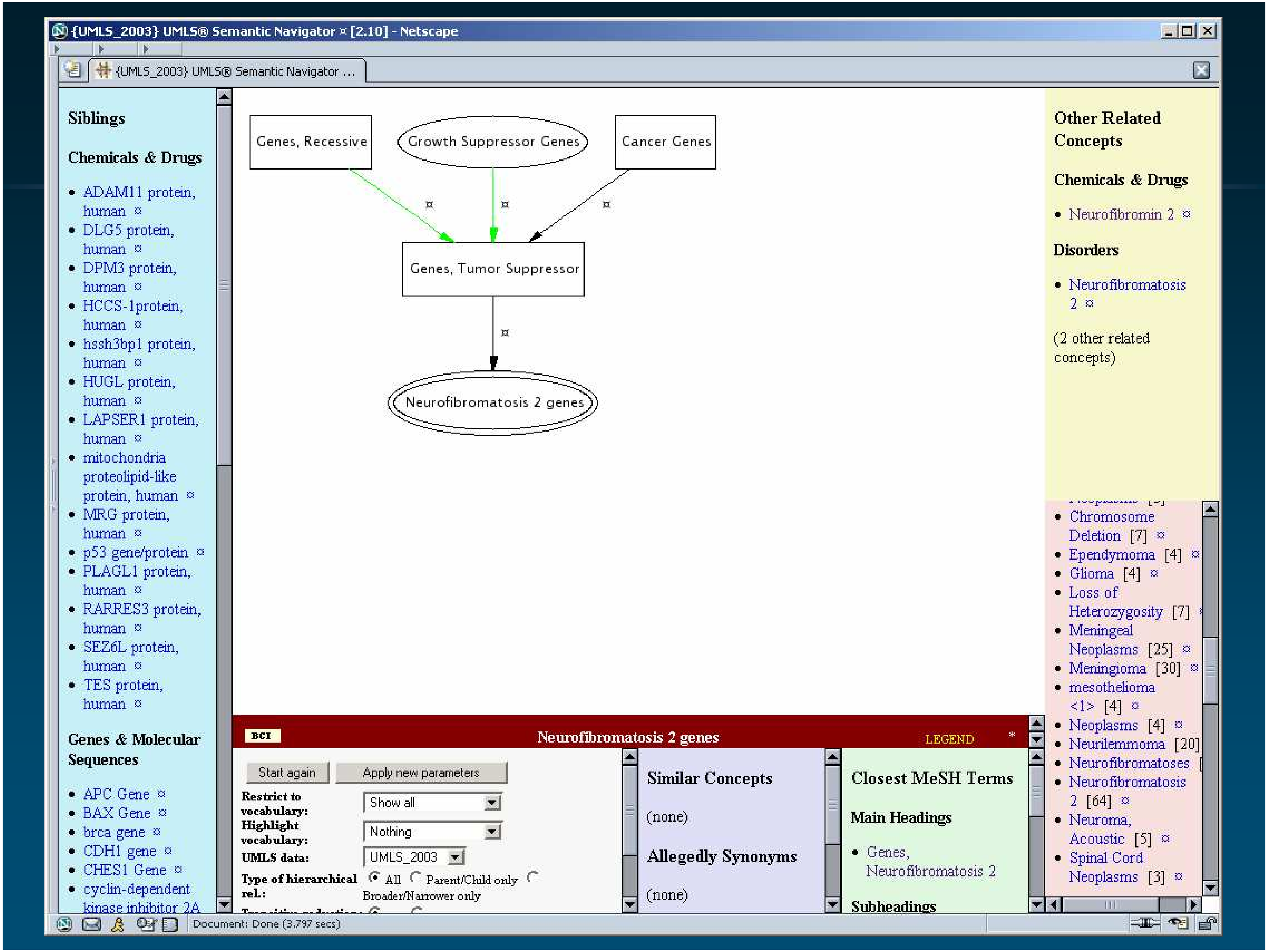
NF2 gene



http://staff.washington.edu/timk/cyto/human/

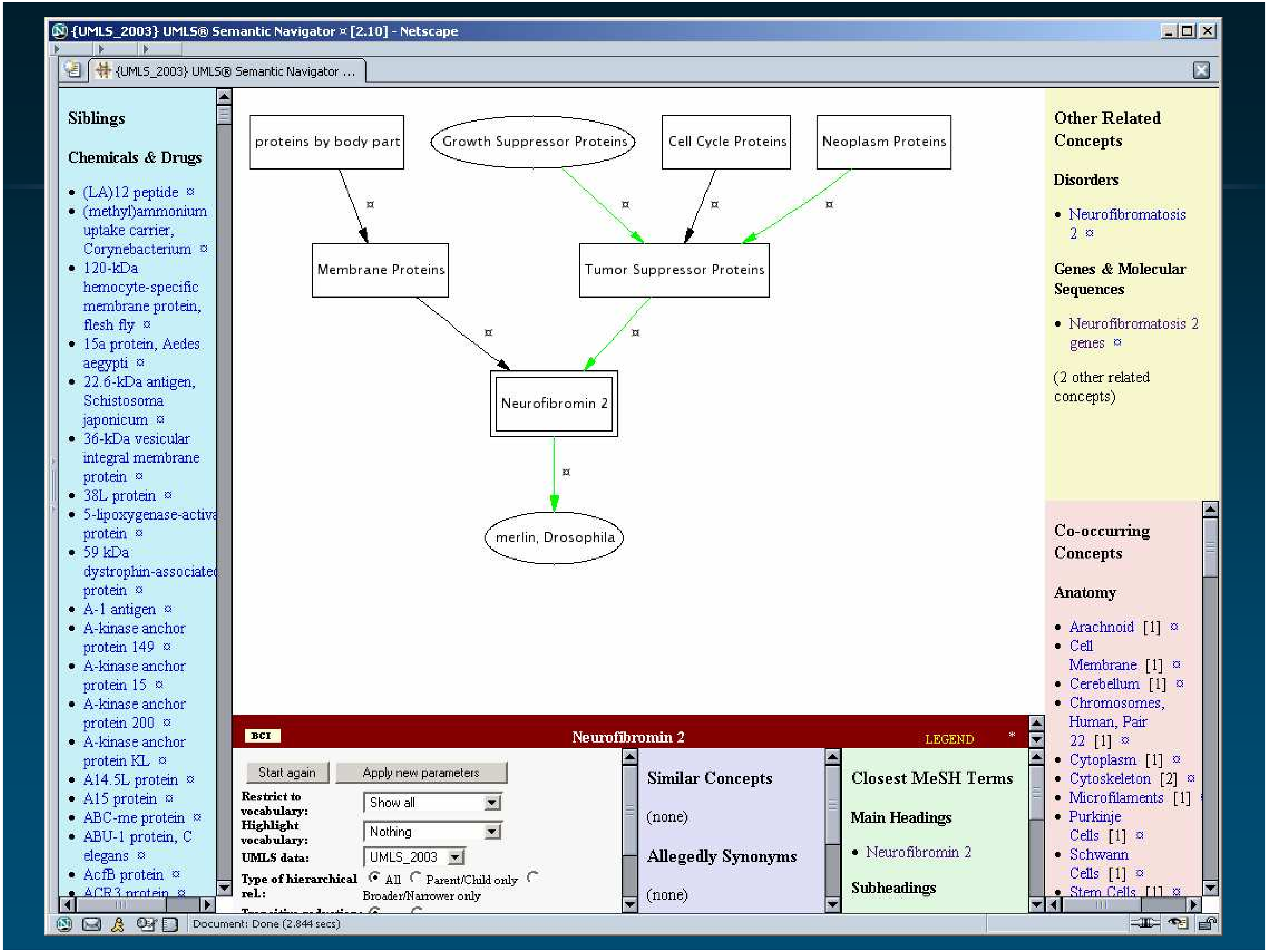


http://www.ncbi.nlm.nih.gov/mapview/


{UMLS_2003} UMLS® Semantic Navigator ¤ [2.10] - Netscape
{UMLS_2003} UMLS® Semantic Navigator ...
Siblings
Chemicals & Drugs
ADAM11 protein, human ¤
DLG5 protein, human ¤
DPM3 protein, human ¤
HCCS-1protein, human ¤
hssh3bp1 protein, human ¤
HUGL protein, human ¤
LAPSER1 protein, human ¤
mitochondria proteolipid-like protein, human ¤
MRG protein, human ¤
p53 gene/protein ¤
PLAGL1 protein, human ¤
RARRES3 protein, human ¤
SEZ6L protein, human ¤
TES protein, human ¤
Genes & Molecular Sequences
APC Gene ¤
BAX Gene ¤
brca gene ¤
CDH1 gene ¤
CHES1 Gene ¤
cyclin-dependent kinase inhibitor 2A
Genes, Recessive
Growth Suppressor Genes
Cancer Genes
Genes, Tumor Suppressor
Neurofibromatosis 2 genes
Other Related Concepts
Chemicals & Drugs
Neurofibromin 2 ¤
Disorders
Neurofibromatosis 2 ¤
(2 other related concepts)
Chromosome Deletion [7] ¤
Ependymoma [4] ¤
Glioma [4] ¤
Loss of Heterozygosity [7]
Meningeal Neoplasms [25] ¤
Meningioma [30] ¤
mesothelioma <1> [4] ¤
Neoplasms [4] ¤
Neurilemmoma [20]
Neurofibromatoses
Neurofibromatosis 2 [64] ¤
Neuroma, Acoustic [5] ¤
Spinal Cord Neoplasms [3] ¤
BCI
Neurofibromatosis 2 genes
LEGEND
Start again
Apply new parameters
Restrict to vocabulary:
Show all
Highlight vocabulary:
Nothing
UMLS data:
UMLS_2003
Type of hierarchical rel.:
All
Parent/Child only
Broader/Narrower only
Similar Concepts
(none)
Allegedly Synonyms
(none)
Closest MeSH Terms
Main Headings
Genes, Neurofibromatosis 2
Subheadings
Document: Done (3.797 secs)

Merlin

- Synonyms
  - Neurofibromin 2
  - Schwannomin
  - Schwannomerlin
  - Neurofibromatosis-2
- 10 isoforms
- Annotations
  - Negative regulation of cell proliferation
  - Cytoskeleton
  - Plasma membrane


{UMLS_2003} UMLS® Semantic Navigator ¤ [2.10] - Netscape
{UMLS_2003} UMLS® Semantic Navigator ...
Siblings
Chemicals & Drugs
(LA)12 peptide ¤
(methyl)ammonium uptake carrier, Corynebacterium ¤
120-kDa hemocyte-specific membrane protein, flesh fly ¤
15a protein, Aedes aegypti ¤
22.6-kDa antigen, Schistosoma japonicum ¤
36-kDa vesicular integral membrane protein ¤
38L protein ¤
5-lipoxygenase-activa protein ¤
59 kDa dystrophin-associated protein ¤
A-1 antigen ¤
A-kinase anchor protein 149 ¤
A-kinase anchor protein 15 ¤
A-kinase anchor protein 200 ¤
A-kinase anchor protein KL ¤
A14.5L protein ¤
A15 protein ¤
ABC-me protein ¤
ABU-1 protein, C elegans ¤
AcfB protein ¤
proteins by body part
Growth Suppressor Proteins
Cell Cycle Proteins
Neoplasm Proteins
Membrane Proteins
Tumor Suppressor Proteins
Neurofibromin 2
merlin, Drosophila
Other Related Concepts
Disorders
Neurofibromatosis 2 ¤
Genes & Molecular Sequences
Neurofibromatosis 2 genes ¤
(2 other related concepts)
Co-occurring Concepts
Anatomy
Arachnoid [1] ¤
Cell Membrane [1] ¤
Cerebellum [1] ¤
Chromosomes, Human, Pair 22 [1] ¤
Cytoplasm [1] ¤
Cytoskeleton [2] ¤
Microfilaments [1]
Purkinje Cells [1] ¤
Schwann Cells [1] ¤
Stem Cells [1] ¤
BCI
Neurofibromin 2
LEGEND
Start again
Apply new parameters
Restrict to vocabulary: Show all
Highlight vocabulary: Nothing
UMLS data: UMLS_2003
Type of hierarchical rel.: All Parent/Child only Broader/Narrower only
Similar Concepts
(none)
Allegedly Synonyms
(none)
Closest MeSH Terms
Main Headings
Neurofibromin 2
Subheadings
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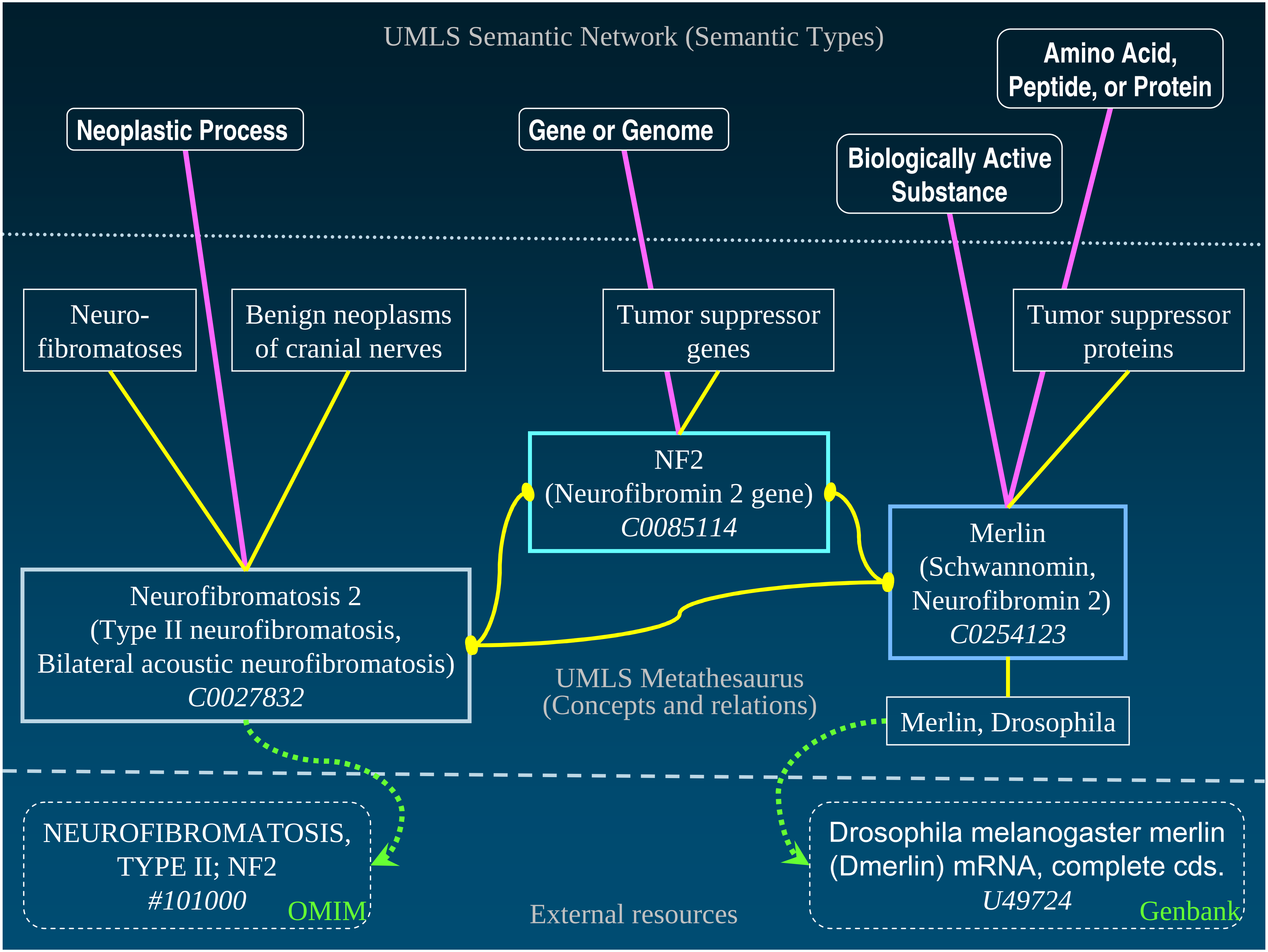

UMLS Semantic Network (Semantic Types)
Amino Acid, Peptide, or Protein
Neoplastic Process
Gene or Genome
Biologically Active Substance
Neuro-fibromatoses
Benign neoplasms of cranial nerves
Tumor suppressor genes
Tumor suppressor proteins
NF2
(Neurofibromin 2 gene)
C0085114
Merlin
(Schwannomin, Neurofibromin 2)
C0254123
Neurofibromatosis 2
(Type II neurofibromatosis, Bilateral acoustic neurofibromatosis)
C0027832
UMLS Metathesaurus
(Concepts and relations)
Merlin, Drosophila
NEUROFIBROMATOSIS, TYPE II; NF2
#101000
OMIM
Drosophila melanogaster merlin (Dmerlin) mRNA, complete cds.
U49724
Genbank
External resources

Limitations

- Genes not systematically represented
  - Most gene products and diseases are
- Gene/Gene product-Disease relations
  - Not systematically represented
  - Not explicitly represented (e.g., co-occurrence)
- Cross-references not systematically represented

- Naming conventions (genes)

Applications (1)

GenesTrace™

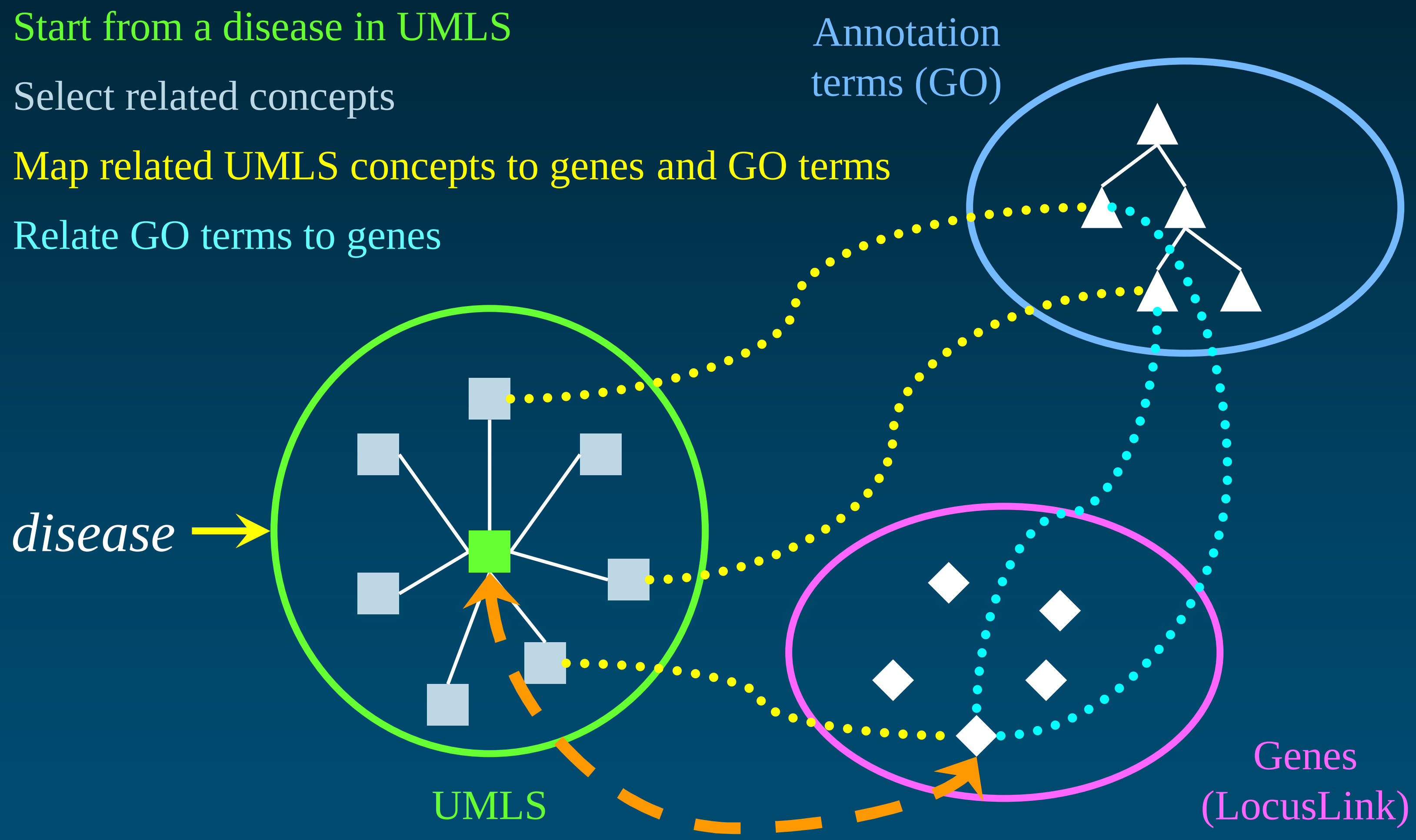
Lussier Lab
Columbia University

Objectives

- Relate diseases to genes through structured, integrated terminologies
- Biological Knowledge Discovery

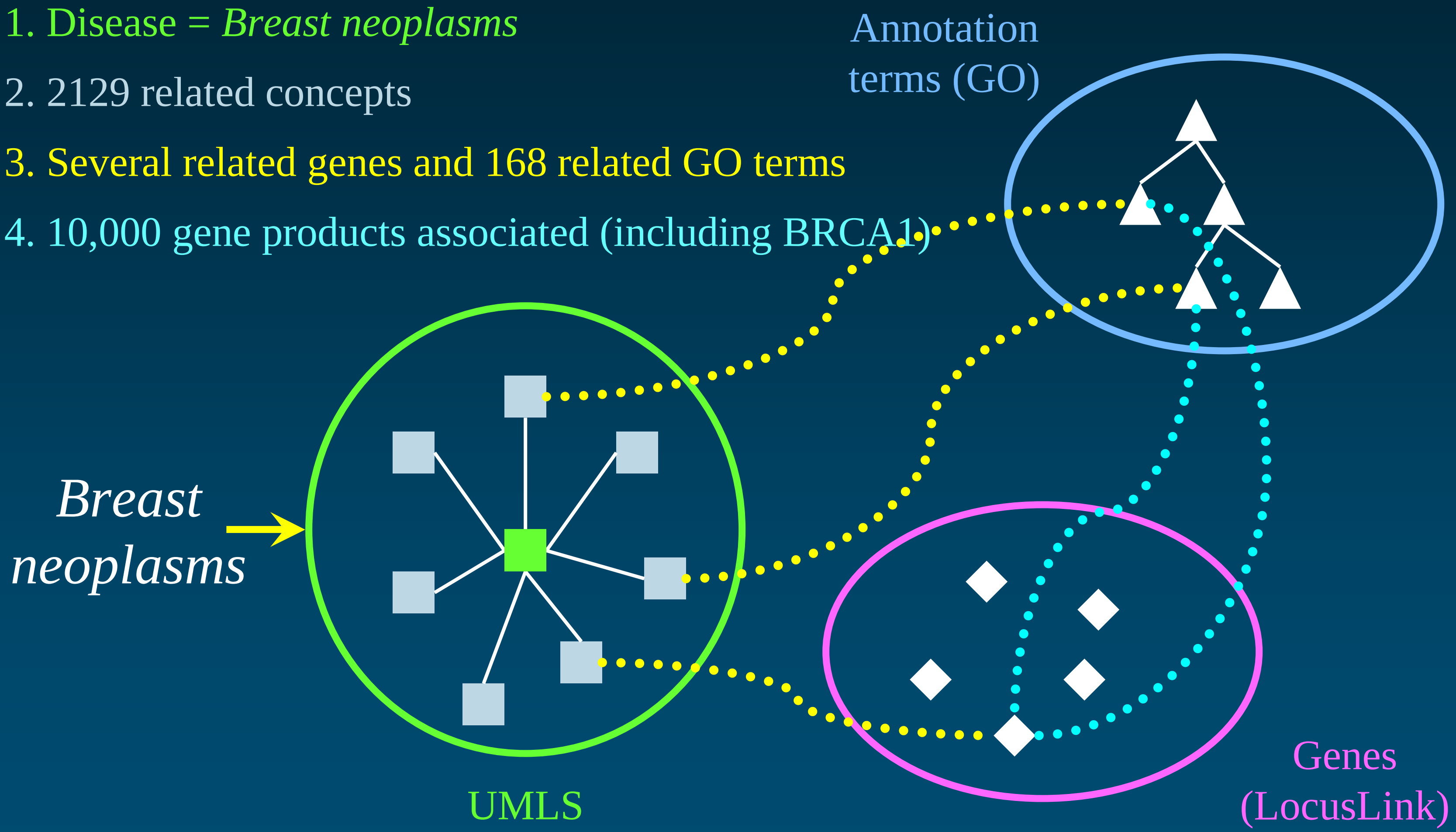
Resources and Methods

1. Start from a disease in UMLS
2. Select related concepts
3. Map related UMLS concepts to genes and GO terms
4. Relate GO terms to genes



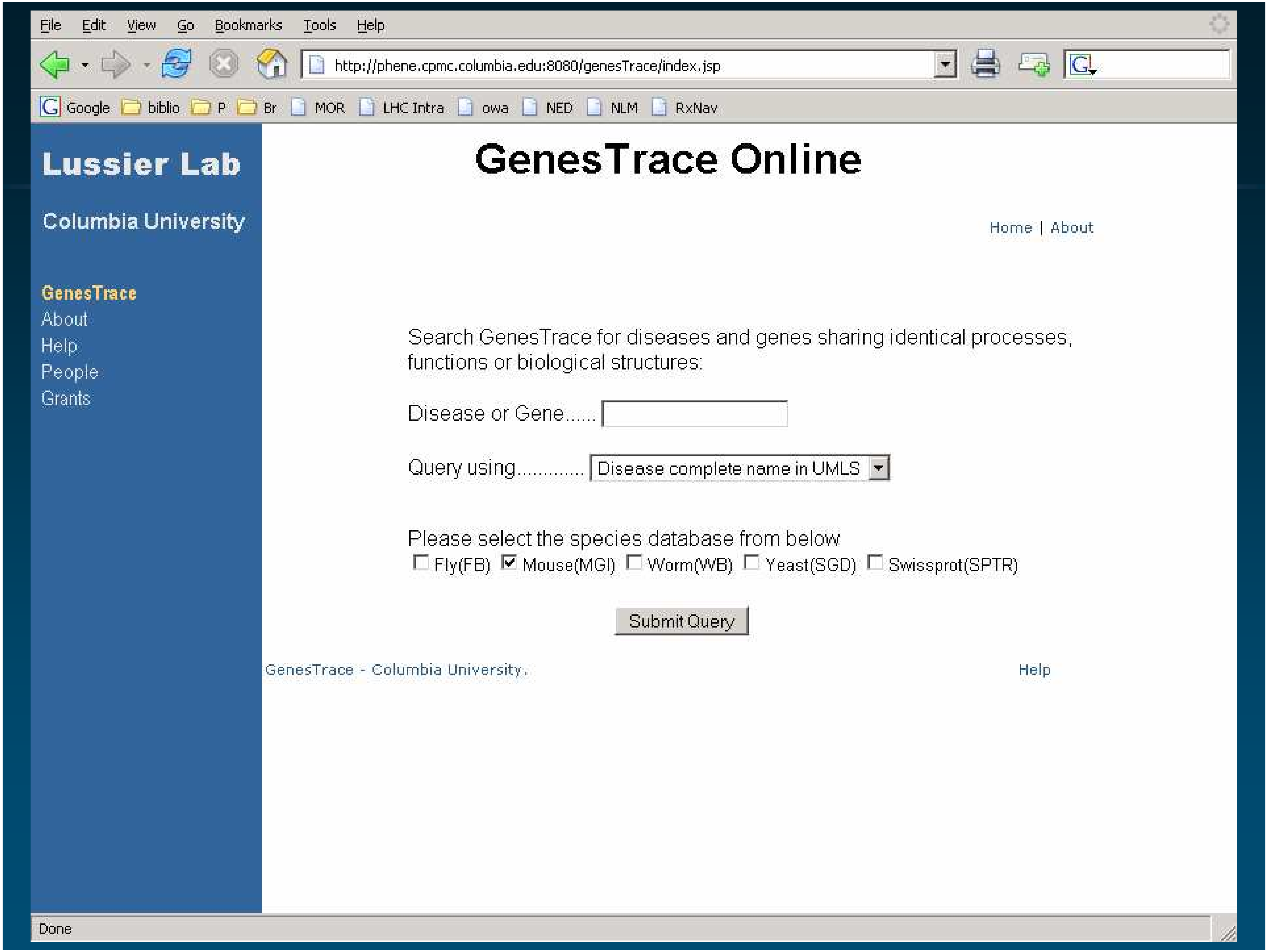
Validation Breast cancer – BRCA1 association

1. Disease = *Breast neoplasms*
2. 2129 related concepts
3. Several related genes and 168 related GO terms
4. 10,000 gene products associated (including BRCA1)



Limitations

- Noise
  - Too many non-specific GO terms associated (e.g., *nucleus*)
  - Too many genes associated
- But
  - Promising preliminary results
  - Room for refinement


File Edit View Go Bookmarks Tools Help
http://phene.cpmc.columbia.edu:8080/genesTrace/index.jsp
Google biblio P Br MOR LHC Intra owa NED NLM RxNav
Lussier Lab
Columbia University
GenesTrace
About
Help
People
Grants
GenesTrace Online
Home | About
Search GenesTrace for diseases and genes sharing identical processes, functions or biological structures:
Disease or Gene......
Query using............ Disease complete name in UMLS
Please select the species database from below
Fly(FB) Mouse(MGI) Worm(WB) Yeast(SGD) Swissprot(SPTR)
Submit Query
GenesTrace - Columbia University.
Help
Done

Applications (2)

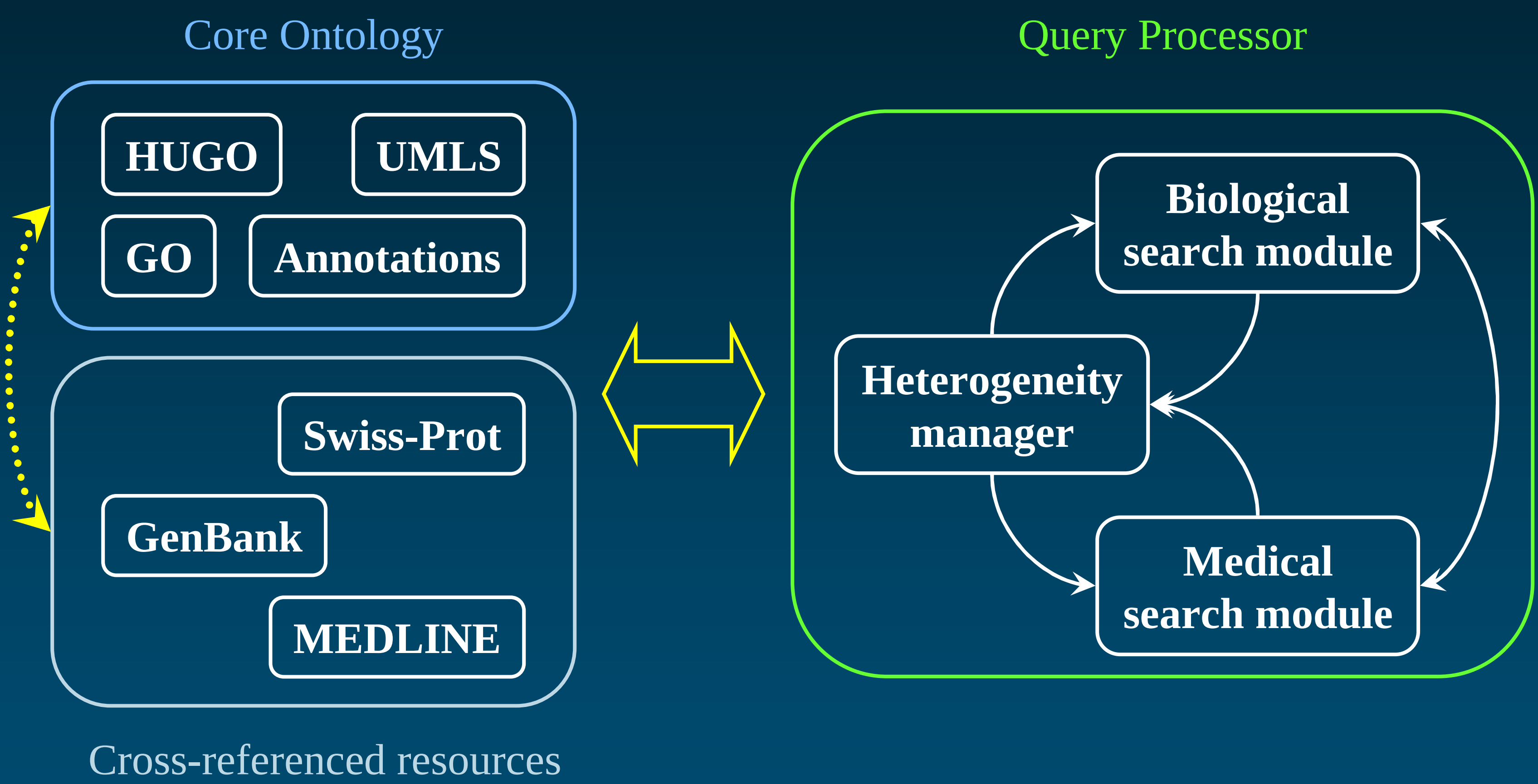
BioMeKe

G. Marquet & al.
LIM, Univ. Rennes, France

Objectives

- To develop a knowledge warehouse for transcriptome analysis (liver diseases)
- Semantic interoperability
  - Medical knowledge bases
    Clinical genomics
  - Molecular biology and genetics knowledge bases
    Functional genomics

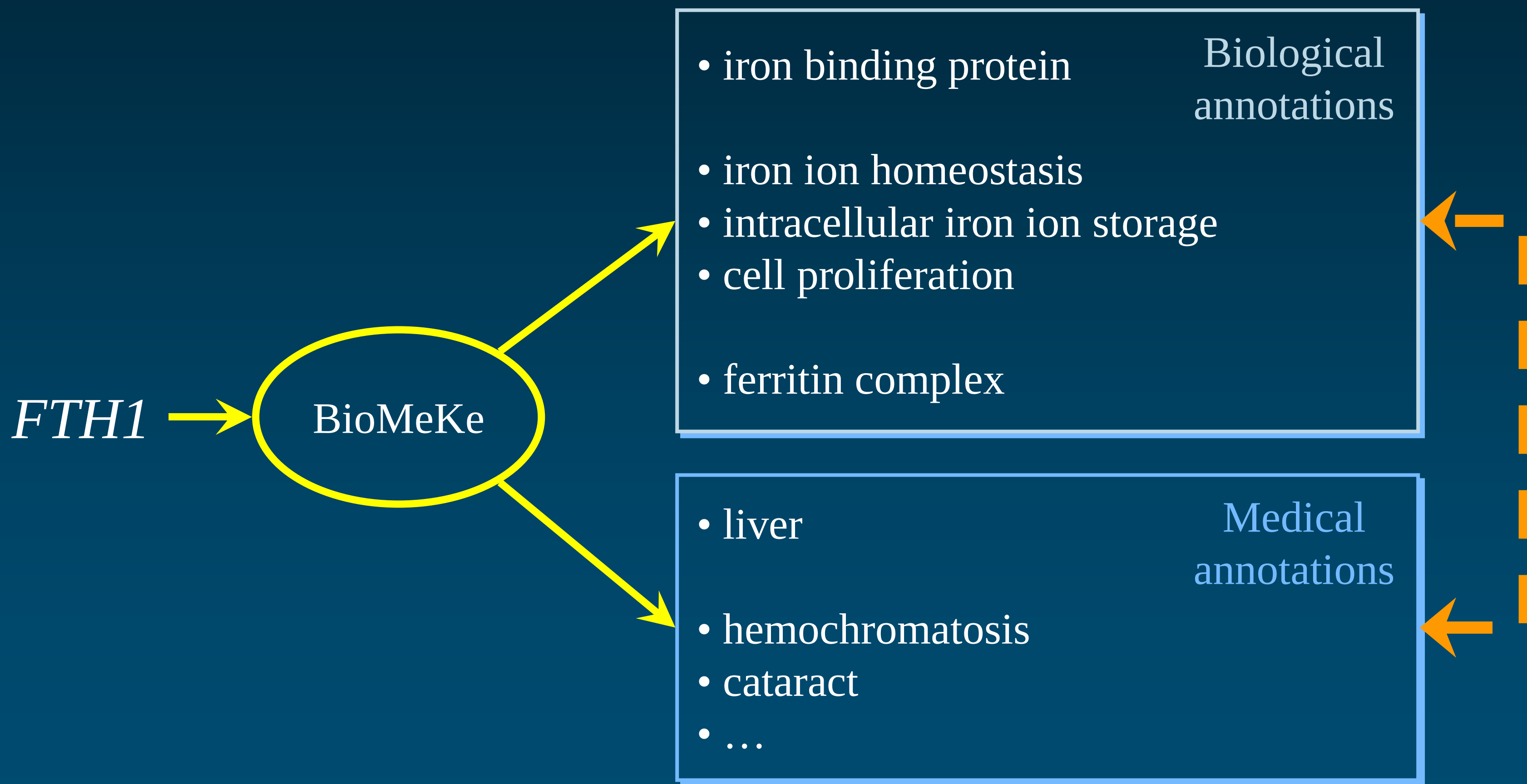
Components


Core Ontology
HUGO
UMLS
GO
Annotations
Swiss-Prot
GenBank
MEDLINE
Cross-referenced resources
Query Processor
Biological search module
Heterogeneity manager
Medical search module

Example

- Input: *ferritin, heavy polypedpide 1*
- Mapping to biological resources
  - Not found in the Core ontology
  - Official name *Ferritin heavy chain* found through Xref
- Biological information obtained from GOA
- Mapping to medical resources
  - Not found in UMLS
  - Synonym *Ferritin H* found through Xref (Swiss-Prot)
- Medical information obtained through co-occurrence of MeSH index terms in MEDLINE

Results


FTH1
BioMeKe
• iron binding protein
• iron ion homeostasis
• intracellular iron ion storage
• cell proliferation
• ferritin complex
Biological annotations
• liver
• hemochromatosis
• cataract
• …
Medical annotations

Limitations

- Non-formal ontologies
  - Knowledge may be inconsistently represented
  - Knowledge may be implicit (mappings)
- Partial automation
  - User input required to select databanks, reformulate queries
- Semantic integration
  - Naming issues
  - Mappings must be updated regularly

File Edit View Go Bookmarks Tools Help

http://www.med.univ-rennes1.fr/~marquet/

Google biblio P Br MOR LHC Intra owa NED NLM RxNav

Lim Laboratoire d'Informatique Médicale

BioMeKe

Inserm unité 522 pathologies biologie

Biological and Medical Knowledge Extraction system

Home

Registration

Download

Installation

Help

Information

Results

References

BioMeKE has been achieved to **extract** and to **associate** Medical and Biological information such as Gene Ontology™, Unified Medical Language System®, Genew ...

BioMeKe is an **ontology-based tool** composed of two-part :

- **Consultation of Ontology and link with Public Databank**
- **Biological and Medical annotation**

Genomic and Biological Resources in BioMeKE:

Genew : Lexical ressources providing official gene names and their synonyms and links to multiple others databases including Uniprot , LocusLink .

Gene Ontology (GO) : general "ontology" for molecular biology which provides a controlled vocabulary for annotationg sequences and genes products.

GeneOntology Annotation@EBI (GOA) : provides assignements of GO terms to genes products for all organisms, including human.

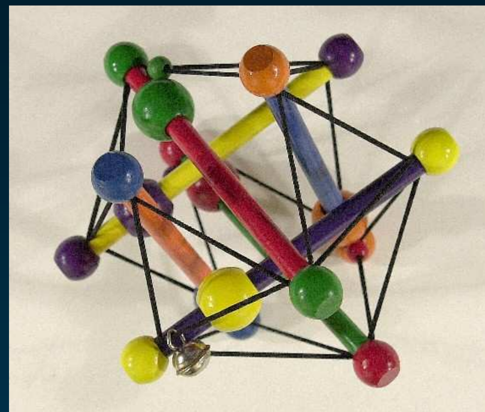
Done

Conclusions

Conclusions

- Terminology integration provides some degree of information integration
- Most terminologies and the cross-referenced databases are readily available

- Lack of consistent representation
- Additional resources/techniques needed



Medical Ontology Research

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NATIONAL LIBRARY OF MEDICINE

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Questions

- What do I need to do to get the UMLS?
- What is an ontology?
- How is ontology different from
  - Terminology? / Database? / Knowledge base?
- Is the UMLS an ontology?
- Does the UMLS use Protégé?
- I heard of OWL. Is that any good?
- What is the Semantic Web going to do for us?

References UMLS

- UMLS
  `umlsinfo.nlm.nih.gov`
- UMLS browser
  - Knowledge Source Server: **`umlsks.nlm.nih.gov`**
  - Semantic Navigator: **`http://mor.nlm.nih.gov/perl/semnav.pl`**
  - (free, but UMLS license required)
- UMLS and information integration
  - O. Bodenreider. The UMLS: Integrating biomedical terminology. *Nucl. Acids Res. 2004;32(1) (in press)*

References Applications

- GenesTrace
  - Cantor MN, Sarkar IN, Bodenreider O, Lussier YA. GenesTrace: Phenomic knowledge discovery via structured terminologies. In: Pacific Symposium on Biocomputing 2005; 2005. (in press).
  - **http://phene.cpmc.columbia.edu:8080/genesTrace/index.jsp**
- BioMeKE
  - Marquet G, Burgun A, Moussouni F, Guerin E, Le Duff F, Loreal O. BioMeKe: an ontology-based biomedical knowledge extraction system devoted to transcriptome analysis. Stud Health Technol Inform. 2003;95:80-5.
  - **http://www.med.univ-rennes1.fr/~marquet/**